

Observational Study

# Health care associated infections, antibiotic resistance and clinical outcome: A surveillance study from Sanandaj, Iran

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**Author contributions:** Soltani J, Poorabbas B, Miri N and Mardaneh J contributions to conception and design, acquisition of data, analysis and interpretation of data; Poorabbas B and Mardaneh J acquisition of data, laboratory performances and interpretation of laboratory data; all authors participated in drafting the article and they critically reviewed the manuscript and approved the final manuscript as submitted.

**Supported by** Kurdistan University of Medical Sciences and Professor Alborzi Clinical Microbiology Research Center affiliated to Shiraz University of Medical Sciences supported the whole study.

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of Professor Alborzi Clinical Microbiology Research Center, Shiraz, Iran. Once again, the study was reviewed and approved by the Institutional Review Board of Research Committee of the Medical Faculty and Research committee of the Kurdistan University of Medical Sciences, Sanandaj, Iran.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** All authors of the paper declare any conflicting interests (including but not limited to commercial, personal, political, intellectual or religious interests) that are related to the work submitted for consideration of publication.

**Data sharing statement:** The technical annex, statistical code, and dataset are available from the corresponding author at [soltanjaf@gmail.com](mailto:soltanjaf@gmail.com). The participants gave informed consent for

the data sharing.

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**Received:** August 4, 2015  
**Peer-review started:** August 6, 2015  
**First decision:** October 16, 2015  
**Revised:** November 9, 2015  
**Accepted:** January 5, 2016  
**Article in press:** January 7, 2016  
**Published online:** March 16, 2016

## Abstract

**AIM:** To study the antibiotic susceptibility patterns of gram-negative healthcare associated bacterial infections at two tertiary hospitals in the Sanandaj city, Kurdistan Province, Iran.

**METHODS:** From January 2012 to December 2012, all positive cultures from potentially sterile body fluids were gathered. They sent to professor Alborzi clinical microbiology center in Shiraz for further analysis and susceptibility testing. The antibiotic susceptibility was determined using the Kirby-Bauer method (disk diffusion

technique). The Results were interpreted according to Clinical and Laboratory Standards Institute guidelines against a series of antimicrobials. World Health Organization definitions for Healthcare associated infections were followed.

**RESULTS:** Seven hundred and thirty-two positive cultures were reported from both hospitals. Seventy-nine isolates/patients fulfilled the study criteria for healthcare associated gram-negative infections. The most frequent bacterial cultures were from the pediatric wards (52%). *Serratia marcescens* (*S. marcescens*) (38%) *Escherichia coli* (*E. coli*) (19%), *Klebsiella pneumoniae* (*K. pneumoniae*) (19%), *Acinetobacter baumannii* (6%), *Enterobacter* species (6%), *Serratia odorifera* (4%) and *Pseudomonas* species (5%) were the most frequently isolated organisms. The susceptibility pattern of common isolates *i.e.*, *S. marcescens*, *E. coli* and *K. pneumoniae* for commonly used antibiotics were as follows: Ampicillin 3.3%, 6.7%, 20%; gentamicin 73.3%, 73.3%, 46.7%; ceftazidim 80%, 73.3%, 33.3%; cefepim 80%, 86.7%, 46.7%; piperacillin/tazobactam 90%, 66.7%, 86.7%; ciprofloxacin 100%, 73.3%, 86.7%; imipenem 100%, 100%, 100%, respectively.

**CONCLUSION:** The most effective antibiotics against gram-negative healthcare associated infections are imipenem followed by ciprofloxacin. The resistance rate is high against ampicillin and cephalothin. The high mortality rate (46.1%) associated with *S. marcescens* is alarming.

**Key words:** *Escherichia coli*; *Klebsiella pneumoniae*; *Serratia marcescens*; Extended-spectrum beta-lactamase; Nosocomial infections; Antibiotic susceptibility

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**Core tip:** To investigate the antibiotic susceptibility patterns of gram-negative healthcare associated bacterial infections a study was conducted in tertiary hospitals in Sanandaj (a large city in the west of Iran). World Health Organization guidelines for hospital-acquired infections were followed. The results were interesting and provided important information concerning antibiotic resistance, making some antibiotics such as cephalothin almost useless. According to our study, gram-negative health care associated infections are challenging especially in pediatric wards. The most effective antibiotics against gram-negative healthcare associated infections were imipenem followed by ciprofloxacin. The high mortality rate (46.1%) associated with *Serratia marcescens* was alarming.

Soltani J, Poorabbas B, Miri N, Mardaneh J. Health care associated infections, antibiotic resistance and clinical outcome: A surveillance study from Sanandaj, Iran. *World J Clin Cases* 2016; 4(3): 63-70 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v4/i3/63.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v4.i3.63>

## INTRODUCTION

Serious bacterial infections that are resistant to commonly available antibiotics have become a major worldwide healthcare problem. They are more severe; require significantly more expensive diagnosis and longer and more sophisticated treatments<sup>[1]</sup>.

Knowledge of the prevalence of antibiotic resistance is a pre-requisite for infection control and essential for public healthcare policy makers to conduct effective responses<sup>[2]</sup>. Currently, a well-organized nationwide surveillance system is only present in three countries/regions, namely United States, European Union and Thailand<sup>[1]</sup>. Some studies indicate high bacterial resistance rates in developing countries<sup>[3-6]</sup>. It is hard to delineate the extent of the problem, since it changes in various healthcare facilities and geographic regions. Most data are retrieved from scattered cross-sectional studies and there is no guideline for rational uses of antibiotics especially at local levels<sup>[7]</sup>. These factors increase the importance of local surveillance pattern of antibiotic resistance from district hospitals. Based on World Health Organization (WHO) guidelines, antibiotic surveillance should be performed in three levels, *i.e.*, local, intermediate and national<sup>[8]</sup>. There is a close relationship between antibiotic resistance and health care associated infections. It is estimated that the nosocomial infection rate and associated mortality rate in developing countries are about 15% and 5%, respectively<sup>[9,10]</sup>. Thirty percent of these rates result from infections caused by gram negative bacteria with a slightly higher rate for mortality<sup>[11]</sup>. Therefore, they are one of the important causes of mortality in developing countries.

A nationwide surveillance system has not yet been established in Iran. Most of the information about antibiotics resistance is retrieved from cross sectional studies. This study was carried out to assess the antibiotic susceptibility patterns of common gram-negative bacteria isolated from infections of normally sterile body sites. The samples collected from two tertiary hospitals called Tohid and Besat located in the Sanandaj city, Kurdistan Province, Iran. They have 1000 beds including all pediatrics and internal medicine subspecialties, gynecology, general surgery, neurology, neurosurgery, cardiology, cardiac surgery, ophthalmology, and otolaryngology wards.

## MATERIALS AND METHODS

Our study was performed from January 2012 through December 2012. Hospital-acquired infections were defined as those occurring 48 h after admission, within 3 d of discharge, or within 30 d of surgery<sup>[10]</sup>. Samples from potentially sterile body fluids [blood, ascitic fluid,

and cerebrospinal fluid (CSF)] were gathered from various wards from Tohid and Besat hospitals. The specimens were sent to the laboratory in a sterile tube for culture. In clinical microbiology laboratory specimens were cultured on general microbiology media including blood agar, chocolate agar, MacConkey agar and EMB agar (Oxoid Ltd, London, United Kingdom) and incubated at 35 °C to 37 °C overnight. For isolation fastidious bacteria culture plates were incubated for one week. Then suspicious colonies were recultured and purified. The isolates were identified by gram staining, catalase test, oxidase test, triple sugar iron fermentation, motility, colony color, pigment production, and odor. All bacteria isolated in Sanandaj were sent to professor Alborzi clinical microbiology center in Shiraz for further analysis and susceptibility testing. The transport medium was blood agar slant prepared in screw-cap tubes. In the center, re-cultivation was performed on previously mentioned microbiology media. For final confirmation, biochemical tests were embedded in the API-20E biochemical kit system (Bio-Mérieux, France) and manual biochemical tests were used, according to the manufacturer's instructions. Strains were preserved at -20 °C on tryptic soy broth (TSB; Oxoid Ltd, London, United Kingdom) containing 20% (v/v) glycerol.

### Susceptibility testing

**Disk diffusion method:** The antibiotic susceptibility testing was determined using the Kirby-Bauer method (disk diffusion technique). The results were interpreted according to Clinical and Laboratory Standards Institute guidelines (CLSI) against a series of antimicrobials<sup>[10]</sup>.

*Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) were tested for aminopenicillin resistance by ampicillin and amoxicillin disks, for aminoglycoside by gentamicin, tobramycin and amikacin disks, for fluoroquinolone resistance by ciprofloxacin, ofloxacin and levofloxacin disks, and for third generation cephalosporins by cefotaxime, ceftazidim and ceftriaxone disks. Susceptibility testing to co-trimoxazole, piperacillin + tazobactam and imipenem/meropenem was also investigated. All isolated of *E. coli* and *K. pneumoniae* that were resistant to third generation cephalosporin were tested for MIC. In the case of an MIC greater than 1 µg/mL, the bacteria were re-tested for extended-spectrum β-lactamase (ESBL) as explained in the following section<sup>[10]</sup>.

### Detection of ESBL in *E. coli* and *K. pneumoniae*

**Combination disk diffusion method:** All *E. coli* and *K. pneumoniae* isolates were screened for ESBL production according to CLSI guidelines using a confirmatory disk diffusion method<sup>[4]</sup> (30 µg) and cefotaxime+clavulanic acid (30 µg + 10 µg), ceftazidime (30 µg) and ceftazidime+clavulanic acid (30 µg + 10 µg) discs (Mast, United Kingdom) were placed at a distance of 25 mm on a Mueller-Hinton Agar plate incubated with a bacterial suspension of 0.5 McFarland turbidity standards and incubated overnight at 37 °C. A ≥ 5 mm increase in

the diameter of inhibition zone for the combination disc vs ceftazidime disc confirmed ESBL production. ESBL producing strain *K. pneumoniae* ATCC 700603 and non-ESBL producing strain *E. coli* ATCC 25922 were used as positive and negative controls.

All *pseudomonas* isolates were tested against a spectrum of antimicrobials including piperacillin, piperacillin + tazobactam, ceftazidime, imipenem, meropenem, ciprofloxacin, levofloxacin, gentamicin, tobramycin, amikacin.

## RESULTS

During one year study, from January 2012 through December 2012, a total of 30334 and 19557 patients were hospitalized in Besat and Tohid tertiary hospitals respectively. Of these, 4320 and 3180 cultures of potentially sterile body fluids were recorded from two hospitals respectively. Totally, 732 positive cultures were reported from both hospitals. Seventy nine isolates/patients fulfilled the study criteria for health-care associated gram-negative infections. Patients had a mean age of 34.12 ± 30.22 years (range, 0-87 years). Thirty-three percent of patients were female. The specimens were obtained from different body sites that were normally sterile. The sources of specimens were as follows: blood, 72 (92.3%); ascitic fluid, 5 (6.4%); and cerebrospinal fluid, 1 (1.3%). The most frequent bacterial cultures were from the pediatrics (52%) and internal medicine wards (29%) and intensive care units (ICU) including pediatric intensive care unit (PICU) (7.5%) (Tables 1 and 2).

*Serratia marcescens* (*S. marcescens*) was the most frequently isolated organism (38%) followed by *E. coli* (19%), *K. pneumoniae* (19%), *Acinetobacter baumannii* (*A. baumannii*) (6%), *Enterobacter* species (6%), *Serratia odorifera* (4%) and *Pseudomonas* species (5%). The remaining isolates included *Stenotrophomonas maltophilia* (one isolate), and *Klebsiella oxytoca* (one isolate). The isolates were tested for antibiotic susceptibility patterns. The profile of antibiotic resistance is shown in Table 3. Overall the susceptibility pattern varied widely. Among antibiotics with systemic uses, the most effective antibiotic was imipenem followed by ciprofloxacin and levofloxacin. The resistance rate was very high against traditional antibiotics such as ampicillin, amoxicillin, and cotrimoxazole.

Thirteen patients expired during the study. The type and frequency of bacteria among expired patients were as follows: *S. marcescens* 6 patients, *E. coli* 3 patients; *K. pneumoniae* 2 patients, *A. baumannii* one patient, and *P. aeruginosa* one patient. The diagnosis of these patients was sepsis in all cases. However, there were other co-morbid underlying diseases in all but one patient. The age prevalence and mortality in each age group were presented in Table 2.

## DISCUSSION

Our study detected 79 cases of nosocomial gram-

**Table 1** Distribution of bacteria isolated from various hospitals wards

Hospital wards Bacteria	Pediatric /neonatal	PICU	Tertiary internal medicine	Infectious diseases	Surgery	General internal medicine	ICU	Total isolates
<i>Escherichia coli</i>	4	0	6	2	2	0	1	15 (19%)
<i>Klebsiella pneumoniae</i>	9	0	2	0	1	2	1	15 (19%)
<i>Acinetobacter baumannii</i>	0	1	4	0	0	0	0	5 (6.3%)
<i>Pseudomonas aeruginosa</i>	1	0	1	0	0	0	0	2 (2.5%)
<i>Pseudomonas oryziabactans</i>	1	0	0	0	0	0	0	1 (1.3%)
<i>Serratia marcescens</i>	20	0	6	2	0	2	0	30 (38%)
<i>Enterobacter cloacae</i>	3	0	0	0	0	1	1	5 (6.3%)
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	1	1 (1.3%)
<i>Klebsiella oxytoca</i>	0	0	0	0	1	0	0	1 (1.3%)
<i>Serratia odorifera</i>	3	0	0	0	0	0	0	3 (3.8%)
<i>Pseudomonas luteola</i>	0	1	0	0	0	0	0	1 (1.3%)
Total isolates in the related wards	41 (52%)	2 (2.50%)	19 (24%)	4 (5%)	4 (5%)	5 (6.5%)	4 (5%)	79 (100%)

PICU: Pediatric intensive care unit; ICU: Intensive care unit.

**Table 2** Prevalence of infections and crude mortality by age groups and isolated organisms *n* (%)

Age groups Bacteria	Neonatal (< 28 d)	Infantile (1-11 mo)	Childhood (1-17 yr)	Adults (18-59 yr)	Elderly (> 60 yr)	Total isolates	Crude mortality by bacteria
<i>Escherichia coli</i>	3 (20) <sup>1</sup>	0	5 (33.3) <sup>1</sup>	2 (13.3) <sup>1</sup>	5 (33.3) <sup>1</sup>	15 (19) <sup>2</sup>	3 (23.1) <sup>3</sup>
<i>Klebsiella pneumoniae</i>	10 (66.7)	0	1 (6.7)	4 (26.7)	0	15 (19) <sup>2</sup>	2 (15.4)
<i>Acinetobacter baumannii</i>	3 (60.0)	0	0	1 (20)	1 (20)	5 (5.6) <sup>2</sup>	1 (7.7)
<i>Pseudomonas aeruginosa</i>	0	1 (50)	1 (50)	0	0	2 (2.2) <sup>2</sup>	1 (7.7)
<i>Pseudomonas oryziabactans</i>	0	0	0	1 (100)	0	1 (1.1) <sup>2</sup>	0
<i>Serratia marcescens</i>	2 (6.7)	6 (20)	11 (36.7)	7 (23.3)	4 (13.3)	30 (33.3) <sup>2</sup>	6 (46.1)
<i>Enterobacter cloacae</i>	0	0	2 (40)	1 (20)	2 (40)	5 (5.6) <sup>2</sup>	0
<i>Stenotrophomonas maltophilia</i>	0	0	0	1 (100)	0	1 (1.1) <sup>2</sup>	0
<i>Klebsiella oxytoca</i>	0	0	0	0	1 (100)	1 (1.1) <sup>2</sup>	0
<i>Serratia odorifera</i>	2 (66.7)	0	1 (33.3)	0	0	3 (3.3) <sup>2</sup>	0
<i>Pseudomonas luteola</i>	0	0	0	0	1 (100)	1 (1.1) <sup>2</sup>	0
Total Isolates in the age groups	20 (25)	7 (8.8)	21 (26.5)	17 (21.5)	14 (17.7)	79 (100)	-
Crude mortality by age	4 (30.8) <sup>3</sup>	0	2 (15.4)	4 (30.7)	3 (23.1)	-	13 (100)

<sup>1</sup>Percent within each isolate; <sup>2</sup>Percent within total isolates of a specific bacteria; <sup>3</sup>Percent within total mortality.

negative infection mostly isolated from blood stream infections (BSIs). The crude mortality rate was calculated as 16.5%. The crude mortality rates that reported in two large series by Marra *et al.*<sup>[12]</sup> and Wisplinghoff *et al.*<sup>[13]</sup> from United States and Brazilian hospitals have been 27% and 40% respectively. The rate of nosocomial BSIs was 16 per 10000 admissions in our hospitals comparing to 60 per 10000 in Wisplinghoff series. Our calculated rates are significantly lower than 2 other series. However, we couldn't deduce strong epidemiological implication because the number of our cases was very low as the duration of our study was shorter comparing to two other studies.

*S. marcescens* was the most common organism isolated in our series at about 38% (Table 2). In series reported by Marra *et al.*<sup>[12]</sup> and Wisplinghoff *et al.*<sup>[13]</sup> the organism comprised only 1.7% and 3.5% of all bacteria isolated from BSIs respectively. Meanwhile, the crude mortality rates were reported as 27.4% and 40% of all deaths respectively. This rate calculated as about 46.1% of crude mortality in our series. The *Serratia* species especially the more pathogen serotype (*S. marcescens*) can cause a spectrum of diseases from urinary tract

infection to meningitis and overwhelming infections<sup>[14]</sup>. It has the potential of being multi-resistant by a variety of mechanisms<sup>[10]</sup>. *S. marcescens* is reported as a nosocomial pathogen that caused outbreaks and endemic healthcare associated infections in many instances<sup>[15]</sup>. The main mechanism of nosocomial spread is hand to hand transmission. Various other ways of transmissions has been reported as important in *Serratia* transmission including contaminated intravenous solution and caps of bottles containing saline, respirators, arterial pressure monitors, suction traps, contaminated hand washing brushes, colonized disinfectants or soaps, contaminated infant parenteral nutrition fluid, and contaminated whole blood or blood products<sup>[15,16]</sup>. High isolation rate especially from pediatric wards (46%) and high mortality rate of *Serratia* in our series are alarming signs. They may be reflective of poor infection control in our hospitals.

The frequency of resistant *Serratia* species to penicillins has been reported to be as high as 90%<sup>[17]</sup>. In our series, the resistance rate for ampicillin and amoxicillin was more than 95%. These high resistance rates are because of the intrinsically resistance chara-

Table 3 Antibiotic susceptibility patterns of gram-negative bacteria isolated from sanandaj hospitals, Iran, 2012 (% susceptible)

	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Klebsiella oxytoca</i>	<i>Serratia marcescens</i>	<i>Serratia ordorifera</i>	<i>Acinetobacter</i>	<i>Species enterobacter</i>	<i>Pseudomonas aeruginosa</i>	<i>Pseudomonas orizihabitans</i>	<i>Pseudomonas luteola</i>	<i>Stenotrophomonas</i>	Susceptibility of all Isolates	No. of isolates tested
Ampicillin	1 (6.7)	3 (20)	0 (0)	1 (3.3)	0 (0)	0 (0)	0 (0)	-	-	-	-	5 (6.7)	74
Amoxicillin	2 (13.3)	1 (6.7)	0 (0)	1 (3.3)	0 (0)	0 (0)	1 (20)	-	-	-	-	5 (6.7)	74
Amikacin	14 (93.3)	8 (53.3)	1 (100)	23 (76.7)	2 (66.7)	2 (40)	4 (80)	2 (100)	1 (100)	1 (100)	1 (100)	58 (73.4)	79
Gentamicin	11 (73.3)	7 (46.7)	0 (0)	22 (73.3)	1 (33.3)	0 (0)	4 (80)	2 (100)	1 (100)	1 (100)	0 (0)	48 (60.7)	79
Tobramycin	-	-	-	-	-	-	-	2 (100)	1 (100)	1 (100)	0 (0)	4 (80)	5
Cotrimoxazole	2 (13.3)	6 (40)	0 (0)	21 (70)	2 (66.7)	1 (20)	4 (80)	0 (0)	0 (0)	0 (0)	0 (0)	36 (45.5)	79
Nitrofurantoin	15 (100)	10 (66.7)	0 (0)	6 (20)	2 (66.7)	0 (0)	3 (60)	-	-	-	-	35 (47.2)	74
Cephalothin	6 (40)	5 (33.3)	0 (0)	1 (3.3)	1 (33.3)	0 (0)	1 (20)	-	-	-	-	13 (17.6)	74
Cefixime	10 (66.7)	5 (33.3)	0 (0)	22 (73.3)	1 (33.3)	0 (0)	2 (40)	-	-	-	-	39 (52.7)	74
Cefotaxime	9 (60)	5 (33.3)	0 (0)	22 (73.3)	1 (33.3)	0 (0)	4 (80)	-	-	-	-	40 (54)	74
Ceftazidim	11 (73.3)	5 (33.3)	0 (0)	24 (80)	2 (66.7)	0 (0)	4 (80)	2 (100)	1 (100)	1 (100)	0 (0)	49 (62)	79
Ceftriaxone	8 (53.3)	6 (40)	0 (0)	22 (73.3)	1 (33.3)	0 (0)	3 (60)	-	-	-	-	39 (52.7)	74
Cefepim	13 (86.7)	7 (46.7)	0 (0)	24 (80)	3 (100)	0 (0)	4 (80)	1 (50)	1 (100)	1 (100)	0 (0)	52 (65.8)	79
Ciprofloxacin	11 (73.3)	13 (86.7)	0 (0)	30 (100)	3 (100)	1 (20)	4 (80)	2 (100)	1 (100)	1 (100)	0 (0)	65 (82.3)	79
Levofloxacin	11 (73.3)	13 (86.7)	0 (0)	30 (100)	3 (100)	1 (20)	5 (100)	2 (100)	1 (100)	1 (100)	1 (100)	67 (84.8)	79
Imipenem	15 (100)	15 (100)	1 (100)	30 (100)	3 (100)	5 (100)	5 (100)	2 (100)	1 (100)	1 (100)	1 (100)	79 (100)	79
Meropenem	-	-	-	-	-	-	-	2 (100)	1 (100)	1 (100)	1 (100)	5 (100)	5
Carbenicillin	-	-	-	-	-	-	-	2 (100)	1 (100)	1 (100)	0 (0)	4 (80)	5
Piperacillin	-	-	-	-	-	-	-	2 (100)	1 (100)	1 (100)	0 (0)	4 (80)	5
Piperacillin/Tazobactam	10 (66.7)	13 (86.7)	1 (100)	27 (90)	3 (100)	0 (0)	4 (80)	2 (100)	1 (100)	1 (100)	-	57 (73)	78
Aztreonam	-	-	-	-	-	-	-	2 (100)	1 (100)	1 (100)	-	3 (75)	4
ESBL(positive)	5 (33.3) <sup>1</sup>	10 (66.7) <sup>1</sup>	-	-	-	-	-	-	-	-	-	16 (51.6) <sup>1</sup>	31 <sup>1</sup>
Total	149 (62.1)	122 (50.8)	3 (18.7)	306 (63.7)	28 (58.3)	10 (12.5)	52 (65)	27 (90)	14 (93.3)	14 (93.3)	4 (30.7)	711 (56.6) <sup>2</sup>	-
susceptible isolates (%)													
Total isolates tested (sum)	240	240	16	480	48	80	80	30	15	15	13	-	1257

<sup>1</sup>Not counted in the sum and susceptibility percents; <sup>2</sup>Total sensitive Isolates (% susceptibility of total tested isolates).

characteristics of the organism as it is the case for penicillin G, amoxicillin-clavulanate, cefuroxime, and narrow-spectrum cephalosporins<sup>[10]</sup>. In fact, these antibiotics are not only ineffective against the *Serratia* species but they are also strong inducers of AmpC gene causing production of ESBL and treatment failure with third generation cephalosporins. Although the early susceptibility testing against third generation cephalosporins may be promising, this organism may become resistant after 3 to 4 d of treatment<sup>[4,18]</sup>. The drug of choice for *Serratia* species is piperacillin. The susceptibility of these organisms in our series to piperacillin-tazobactam was between 90%-100% (mean: 91%). The susceptibility of *Serratia* for ciprofloxacin, levofloxacin, and imipenem were 100% making them advisable beside piperacillin in treating overwhelming infection caused by *Serratia* species. These sensitivity rates are comparable to findings by Wisplinghoff *et al.*<sup>[13]</sup> from United States. They reported the sensitivity rates of *Serratia* to traditional antibiotics ranged from 83.2% to 97.4%. The susceptibility of *Serratia* to cefepim in our study was lower (80%). Overuse of this antibiotic as an empirical choice in our hospitals may be the cause of lower susceptibility<sup>[19]</sup>. Moderate susceptibility of *Serratia* species to aminoglycosides ranging from 33% to 77% (mean: 73%) make these antibiotics optional for synergistic use with other antibiotics in our district.

*E. coli* and *K. pneumonia* were the second most common group of isolated bacteria. Each bacterium comprised 19% of total isolates in our series. It is more than the rate reported by larger studies at about 4.8% to 13.2%<sup>[12,13]</sup>. The source of infection was blood stream mostly from pediatric and neonatal wards (43%) followed by internal medicine (33%). *E. coli* is the most common causes of neonatal sepsis. Most infections of *K. pneumonia* are acquired in hospital. It is a common cause of neonatal septicemia with high mortality rate. The susceptibility of these organisms to ampicillin and amoxicillin were poor ranging from 6.7% to 20%. These rates may be comparable to the rates reported for *K. pneumonia* (2%-45.5%), however it is far less than the susceptibility rates for *E. coli* (54.2%) in other series<sup>[12,13]</sup>. The susceptibility rates of *E. coli* and *K. pneumonia* to gentamicin in our series were calculated as 73.3 and 46.7 respectively. These rates are far less than rates from United States reported as 96.1% and 84% respectively<sup>[13]</sup>. The current WHO recommendation for empirical prophylaxis and treatment of suspected neonatal sepsis is a combination of ampicillin and gentamicin<sup>[20]</sup>. The quality of evidence for the recommendation of sepsis prophylaxis is categorized as weak and very low quality evidence; and for sepsis treatment is categorized as strong and low quality of evidence. Nevertheless, the efficacy of this antibiotics combination should be re-assessed considering the higher resistance rates to ampicillin and gentamicin in Iran. The susceptibility rate of *E. coli* to ciprofloxacin was 73% compared to previous reports from Iran that measured it at about 46%. The susceptibility rates to third generation cephalosporins were ranged from 53% to 73%. The previous reports from Iran denoted a susceptibility rate to third generation cephalosporins of about 59%<sup>[11]</sup>. Lower susceptibility to cotrimoxazole and cefixime reflects higher use of the antibiotic in outpatient oral therapy of UTI and gastroenteritis in children. However, low resistance rate of *E. coli* against nitrofurantoin may be due to its infrequent use as a urinary antiseptic and no application in systemic infection.

There are wide therapeutic options for nonresistant cases of *K. pneumonia*. However this is limited to fourth generation cephalosporins and carbapenems for multi-resistant cases<sup>[21]</sup>. The clinical response to various antibiotics is largely determined by ESBL production by this organism rather than early *in vitro* susceptibility patterns<sup>[18]</sup>. The rates of ESBL production by *E. coli* and *K. pneumonia* were 33.3% and 66.7%, respectively. Surprisingly, these rates are much lower than the rates reported for European countries (72.7%-100%) and Brasilia (72.3%-91.4%)<sup>[12,22]</sup>. This difference could be attributed to the different methodologies used in these studies. We had tested all isolates for ESBL production while the other 2 studies had tested only selected bacteria that had been resistant to third generation cephalosporins from selected laboratories. Resistance rates of *E. coli* and *K. pneumonia* to beta-lactam

antibiotics were parallel to ESBL production rates. The susceptibility rates of *K. pneumonia* to 3<sup>rd</sup> generation cephalosporins ranged from 33%-40% while these numbers for *E. coli* species were between 53% and 73.3%. Previous reports from Iran has been calculated the susceptibility of *K. pneumonia* to 3<sup>rd</sup> generation cephalosporins at 52%<sup>[11]</sup>. The susceptibility rate for cefepim was similar to 3<sup>rd</sup> generation cephalosporins. Fortunately, the susceptibility to imipenem for *K. pneumonia* was very high (100%) making this antibiotic the drug of choice for difficult-to-treat infections in our community. This susceptibility rate is much higher compared to previously reported data from Iran (46%)<sup>[11]</sup>. The resistance rate of *K. pneumonia* to carbapenems in some countries has been reported worrisome<sup>[12]</sup>.

The isolation rate for *Acinetobacter* was 6%, mostly recovered from internal medicine and pediatrics wards. This figure may sound alarming because of its higher rate in comparison with other studies. The reported isolation rates for *Acinetobacter baumannii* were as 1.3% and 2.7% from two large series from United States<sup>[2,13]</sup>. However, because of the relatively lower number of total isolated bacteria and short period of our study, the comparison of prevalences may be statistically inaccurate. It should be noted that once the multi-resistant *Acinetobacter* is introduced into a hospital, it could cause recurrent outbreaks and prolonged colonization<sup>[23]</sup>. It can remain alive under a wide range of environmental conditions<sup>[24]</sup>. This organism has the potential to be multi-resistant, and the related infections are very difficult to treat. The susceptibility rates reported for *Acinetobacter* from different European countries have been very wide ranged from 4.2% (Romania) to 100% (the Netherlands)<sup>[14]</sup>. The susceptibility rates for *Acinetobacter* were low in our series. These rates were mostly below 40% (Table 3). However, in contrast to many reports of increasing resistance to imipenem<sup>[2,4,5]</sup>, *Acinetobacter* remained highly susceptible to imipenem (100%) in our hospitals. The resistance rate and prevalence of this organism as a cause of ventilator associated pneumonia is increasing steadily in many countries<sup>[11]</sup>. However, most of our isolates (80%) were not from ICU wards. The combination of colistin and rifampin, imipenem and rifampin or amikacin may be good choices for multi-resistant *Acinetobacter* in our community<sup>[11,24]</sup>.

The *enterobacter* species accounted for 6% of isolated bacteria. This rate is comparable to rates of isolation from three large series that ranged from 3.9% to 6.1%<sup>[2,5,12,13]</sup>. Our isolates comprise 5 cases of *Enterobacter cloacae*. In large series, *Enterobacter cloacae* was the most common species isolated from clinical samples<sup>[25]</sup>. Inducible resistances to 3<sup>rd</sup> generation cephalosporins by previous use of aminopenicillin and some other antibiotics is a major determinant for selection of antibiotics. Similar to *Serratia*, antibiotic resistance may develop during treatment despite early susceptibility reports. In our series, the organism preserved good susceptibility against imipenem and levofloxacin by

100% susceptibility and against ciprofloxacin, ceftazidim and cefotaxime, cefepim, amikacin, gentamicin, cotrimoxazole and piperacillin-tazobactam by 80% susceptibility.

We found only 4 isolates for *Pseudomonas* species. These comprised two positive cultures for *Pseudomonas aeruginosa*, one for *Pseudomonas orizihibitans* and one for *Pseudomonas luteola*. They were isolated from pediatric ward (2 isolates), internal medicine and ICU (each one isolate). Unexpectedly, they were susceptible to most antibiotics tested. One case was resistant to cefepim. The high susceptibility rates are in contrast to reports from many other studies<sup>[2,25,26]</sup>. However, the number of isolates was too low to derive a defensible statistical inference. The bacteria may be isolated from new hospitalized patients suffering from community acquired infection and therefore might preserve their primary antibiotics susceptibility. One exception was resistance to cotrimoxazole by all isolates of pseudomonas. High use of cotrimoxazole as a urinary disinfectant and in the treatment of gastroenteritis in Iran may be an explanation for this finding<sup>[11,25]</sup>.

We had only one case of *Stenotrophomonas maltophilia*. This organism has the inherent potential to be resistant to many available antibiotics. Cotrimoxazole has been proposed as the drug of choice for the treatment of multi-resistant isolations<sup>[27]</sup>. However, our isolate was resistant to cotrimoxazole, all Aminoglycosides except amikacin, and many other antibiotics (Table 3).

There are many studies denoting a considerable association between the rate of antibiotic consumption and bacterial resistance pattern both in the hospital and community<sup>[4,6,28,29]</sup>. It has been proposed that a reduction in antibiotic use would decrease the rate of bacterial resistance<sup>[4,30]</sup>. Therefore, there is a need to emphasize the judicious use of antimicrobials and pay adequate attention to the subject of "reserve drugs"<sup>[25]</sup>.

Continuous antimicrobial surveillance is necessary to determine the changing status of antibiotic resistance in local, provincial and national referral hospitals. Effective strategies/guidelines should be established to minimize the misuse of existing antimicrobials.

Our study was performed using data collection from two large hospitals in Sanandaj for one year; however the number of isolate were not enough to conclude strong epidemiological deduction. A study with a longer duration based on a detailed surveillance system is needed to monitor antibiotic resistance continuously.

We found a high bacterial resistance rate isolated from healthcare associated infections in our hospitals. The most effective antibiotics against gram-negative healthcare associated infections were imipenem followed by ciprofloxacin. The resistance rate was high against ampicillin and cephalothin. The high mortality rate (46.1%) associated with *S. marcescens* was alarming. A national surveillance program is essential to monitor the extent of resistance continuously, emphasize rational use of antimicrobials, and conduct effective measures to improve patient management outcome.

## ACKNOWLEDGMENTS

The authors thank Dr. Daem Roshani, Assistant Professor (PhD) of Biostatistics affiliated to Faculty of Medicine, Kurdistan University of Medical Sciences for his compassionate accompaniment and careful review of the article and also thank laboratory personnel in the department of Professor Alborzi Clinical Microbiology Research Center in Shiraz University of Medical Sciences.

## COMMENTS

### Background

Knowledge of the prevalence of antibiotic resistance is a pre-requisite for infection control and essential for public healthcare policy makers to conduct effective responses. A nationwide surveillance system has not yet been established in Iran. Most data are retrieved from scattered cross-sectional studies and there is no guideline for rational uses of antibiotics especially at local levels. It is hard to delineate the extent of the problem, since it changes in various healthcare facilities and geographical regions.

### Research frontiers

In recent years, the status of antibiotic resistance has changed very rapidly. Iran had one of the highest antibiotic consumption rates. Fears regarding that the irrational use of antibiotics have resulted in a high level of antibiotic resistance. Few studies from Iran indicate high resistance rate. No antibiotic stewardship has yet been established in this country.

### Innovations and breakthroughs

The present study is the only evidence based data from this county. It was carried out to assess the antibiotic susceptibility patterns of common gram-negative bacteria isolated from infections of normally sterile body sites. The patients were from two tertiary hospitals called Tohid and Besat located in the Sanandaj city, Kurdistan Province, Iran. The study was performed from January 2012 through December 2012.

### Applications

The data in this study recommended that antibiotic resistance is alarming in this county. Moreover, this study also provided readers with important information regarding the clinical implication of current status of antibiotic resistance.

### Terminology

Sanandaj is the center of Kurdistan province in the west of Iran with a population of about 480000. The samples were collected from two tertiary hospitals called Tohid and Besat located in the Sanandaj. They have 1000 beds including all pediatrics and internal medicine subspecialties, gynecology, general surgery, neurology, neurosurgery, cardiology, cardiac surgery, ophthalmology, and otolaryngology wards.

### Peer-review

Available papers concerning antimicrobial resistance in Sanandaj are scarce. The authors in this study analyzed the characteristics and outcomes of infections of sterile body sites especially blood stream infection. This study showed that the most effective antibiotics against gram-negative healthcare associated infections were imipenem followed by ciprofloxacin. The results were interesting and provided important information concerning antibiotic resistance, making some antibiotics such as cephalothin almost useless. The high mortality rate (46.1%) associated with *Serratia marcescens* was alarming.

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